Cirrhosis Pharmacotherapy Summary

Based on the AFP guideline on cirrhosis (2019), AASLD guidelines on portal hypertensive bleeding (2016) and ascites/SBP/HRS (2021), and AASLD/EASL guideline on hepatic encephalopathy (2014)

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Overview of Cirrhosis

What is cirrhosis?

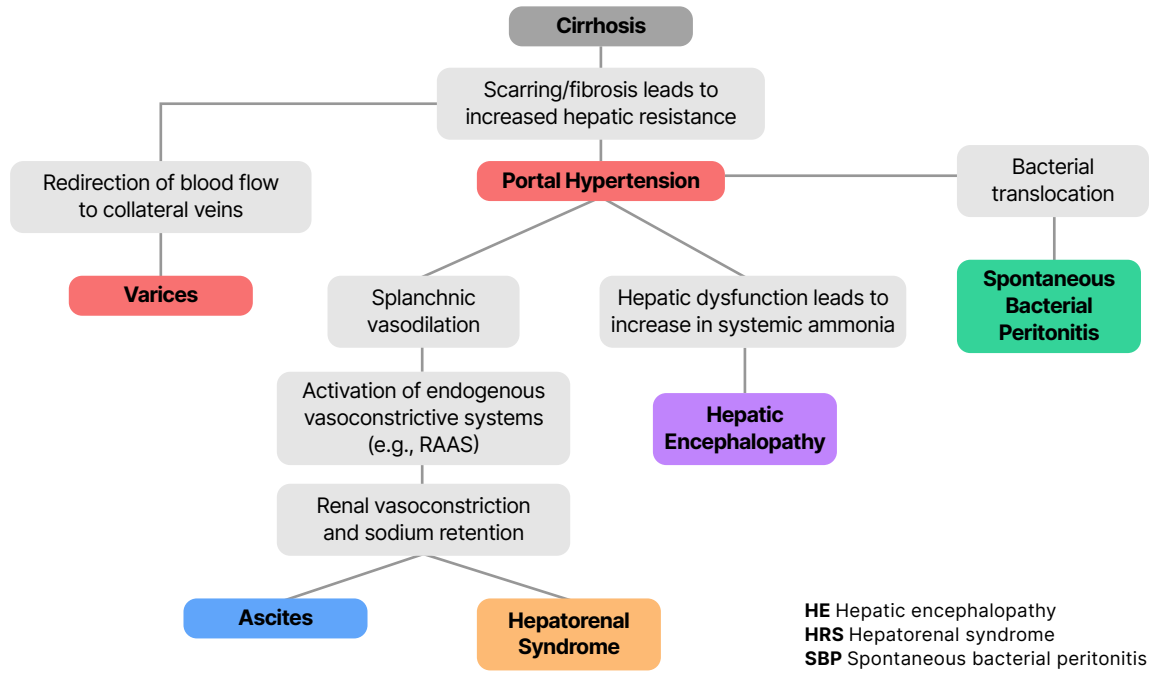
- **End-stage** of chronic liver disease
- Characterized by **advanced fibrosis/scarring**
- Complications include portal hypertension, varices, ascites, HE, HRS, SBP, liver cancer, and liver failure
- Common causes: alcohol-associated liver disease, chronic viral hepatitis infection, nonalcoholic fatty liver disease
- Diagnosed by **liver biopsy** (gold standard but invasive) or clinical findings (imaging, labs, medical history, presentations)

Classification of cirrhosis

- Child-Turcotte-Pugh (**CTP**) or Child-Pugh (**CP**) score assesses stage and severity of cirrhosis
  - Considers total bilirubin, albumin, INR, and degree of ascites and encephalopathy
  - Classifies into A (compensated), B (early decompensated), or C (severely decompensated)
- Model for End-Stage Liver Disease (**MELD**)score assesses prognosis (3-month mortality) for patients with cirrhosis
  - 12 or higher predicts increased risk of complications

Goals of therapy

- Prevent complications of cirrhosis
- Prevent hepatic decompensation
- Reduce mortality



HE Hepatic encephalopathy
HRS Hepatorenal syndrome
SBP Spontaneous bacterial peritonitis

Portal Hypertension (PH) & Varices

- Scarring of liver impedes blood flow through portal vein, increasing the blood pressure
  - **Varices** = distension in collateral vessels from redirected blood; at risk of **variceal hemorrhage**
- PH defined as **hepatic venous pressure gradient (HVPG) > 5 mmHg**
  - HVPG = difference in pressure between portal vein and hepatic veins
  - HVPG ≥ 10 mmHg = **clinically significant portal hypertension (CSPH)**
- **Primary prophylaxis of variceal hemorrhage**
  - A beta-blocker (**propranolol** 20-40 mg twice daily, **nadolol** 20-40 mg once daily, or **carvedilol** 6.25 mg twice daily) continued indefinitely, **OR**
  - Endoscopic variceal ligation (**EVL**) every 2-8 weeks until variceal eradication
- **Treatment of acute variceal hemorrhage**
  - **IV ceftriaxone (**1 g/day x max 7 days) + **EVL** + a vasoactive drug (see below)
    - **Octreotide**: 50 mcg bolus → continuous infusion at 50 mcg/hr for 2-5 days, **or**
    - **Vasopressin**: continuous infusion at 0.2-0.4 units/min (max 0.8 units/min) for 24 hours + concurrent IV nitroglycerin to maintain SBP of 90 mmHg, **or**
    - **Terlipressin**: 2 mg IV every 4 hours during the first 48 hours to control bleeding, then 1 mg every 4 hours to prevent rebleeding (total duration 2-5 days)
- **Secondary prophylaxis of variceal hemorrhage**
  - A non-selective beta-blocker (**propranolol** 20-40 mg twice daily or **nadolol** 20-40 mg once daily) continued indefinitely, **AND**
  - **EVL** every 1-4 weeks until variceal eradication

Ascites

- Accumulation of **excess fluid** in the abdomen; often the first decompensating event
- **Dietary sodium restriction (to 2 g/day)** recommended for net fluid loss
- **Diuretic therapy (aldosterone antagonist + loop diuretic)**
  - **Preferred**: spironolactone + furosemide
  - Initially **spironolactone 100 mg + furosemide 40 mg per day**
  - Titrate to maximum of spironolactone 400 mg + furosemide 160 mg per day
  - At least **72-hour interval** needed between dose titrations
  - Taper down to the lowest effective dose after fluid is adequately mobilized
- Monitor daily body weight to assess efficacy of diuretics
  - Up to **0.5 kg/day weight loss** is generally appropriate (up to 1 kg/day for those with edema)

Spontaneous Bacterial Peritonitis (SBP)

- Often no clear source of infection; mainly Gram-negative bacteria (*E. coli*, *K. pneumoniae*) but some Gram-positive organisms can be common (*S. aureus*, *E. faecalis*, *E., faecium*)
- **Diagnosis:** polymorphonuclear (PMN) leukocyte > 250/mm3 in the ascitic fluid
- **Treatment: antibiotic therapy + IV albumin**
  - Empiric 3rd-gen cephalosporin (e.g., **ceftriaxone**, **cefotaxime**) generally recommended
  - **Broad spectrum** agents (e.g., **piperacillin/tazobactam**) recommended for healthcare-associated or nosocomial infection, those with recent exposure to broad-spectrum abx, or those admitted with sepsis/septic shock
  - Add **vancomycin** if prior MRSA infection or positive MRSA swab
  - Add **daptomycin** for vancomycin-resistant enterococcus
  - **Meropenem** +/- glycopeptide if current or recent exposure to piperacillin/tazobactam
  - Repeat diagnostic paracentesis **48 hours** from initiation; PMN decrease of **< 25%** from baseline may require broadening of antibiotic therapy or investigation of secondary peritonitis
- **Secondary prevention**
  - Long-term prophylaxis with **ciprofloxacin** 500 mg/day
- **Primary prevention**
  - IV ceftriaxone for patients with variceal hemorrhage (see PH & Varices section)
  - Generally only needed if high risk of infection present
  - **Ciprofloxacin** for patients with low ascitic fluid protein (< 1.5 g/dL) + and renal dysfunction or liver failure

Hepatorenal Syndrome (HRS)

- Renal complication due to hemodynamic changes and systemic inflammation associated with cirrhosis
- **Diagnosis of HRS-AKI (acute kidney injury from HRS)**
  - Cirrhosis with ascites
  - Diagnosis of AKI (↑ SCr by ≥ 0.3 mg/dL in 48 hr OR ≥ 50% ↑ in SCr in the past 7 days)
  - No response after 2 consecutive days of diuretic withdrawal & plasma volume expansion with albumin infusion
  - No current/recent use of nephrotoxic drugs, structural kidney injury, or shock
- **Treatment of HRS-AKI**
  - Vasoconstrictor (**terlipressin** preferred; **norepinephrine** also recommended) + **albumin**
  - Decrease in SCr to < 1.5 mg/dL or return to baseline within 0.3 mg/dL over maximum of **14 days** indicates **successful response**

Hepatic Encephalopathy (HE)

- Believed to be due to ammonia accumulation caused by hepatic dysfunction
- **Symptoms:** impaired memory and motor function, **asterixis ("flapping tremor")**, personality changes, coma
- Categorized with West Haven criteria (WHC grades 1 to 4)
- Diagnosed by excluding other causes of cognitive dysfunction
- **Short-term** protein restriction may be necessary for nitrogen modulation
- Treatment recommended for fully symptomatic overt HE
  - **Lactulose** (nonabsorbable disaccharide): preferred treatment
    - 30-45 mL every 1-2 hours until at least 2 soft stools/day are produced
    - Thereafter, titrated to maintain 2-3 soft stools/day
  - **Rifaximin** (add-on to lactulose) to **prevent** HE recurrence after **second** episode
    - 550 mg twice daily

Reference:
[1] American Association for the Study of Liver Diseases; European Association for the Study of the Liver. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. J Hepatol. 2014 Sep;61(3):642-59. doi: 10.1016/j.jhep.2014.05.042. Epub 2014 Jul 8. Erratum in: J Hepatol. 2015 Oct;63(4):1055.
[2] Biggins SW, Angeli P, et al. Diagnosis, evaluation, and management of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome: 2021 Practice guidance by the American Association for the Study of Liver Diseases. Hepatology. 2021 Aug;74(2):1014-1048. doi: 10.1002/hep.31884.
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[4] Smith A, Baumgartner K, et al. Cirrhosis: Diagnosis and management. Am Fam Physician. 2019;100(12):759-770.

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